FIGURE 2.—Trends in 30-day prevalence of daily cigarette
use (smoking one or more cigarettes/day)
among high school seniors, by sex

decline noticed in adults (see Tables 1, 3). However, the rate of
decline has tapered off in recent years. The smoking rates among
females have consistently exceeded the rates among males.

The Monitoring of the Future Project has also followed representa-
tive samples from each graduating class since 1976. This was done by
selecting two matched panels from each graduating class and
following each panel in alternate years. The data obtained from
these surveys are presented in Figure 3. Recently, differences in
prevalence of any cigarette smoking within the last 30 days has
disappeared between those still in high school and those who have
graduated, suggesting that far fewer young adults are taking up
smoking after high school, and that most uptake has occurred by the
time of high school graduation. However, when either the 30-day
prevalence of daily use or the 30-day prevalence of the use of half a

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pack or more per day is considered, there is a clear marked increase in smoking prevalence in the early years after high school, suggesting that occasional and experimenting high school smokers become regular smokers once they leave school.

## Trends in the Proportion of Smokers Who are Heavy Smokers

The average reported number of cigarettes smoked per day in 1985 by age, race, and sex is presented in Table 9. There are marked differences between the black and white population in the number of cigarettes reported. Both black males and females report smoking one-third fewer cigarettes per day than do their white counterparts. Even though blacks smoke fewer cigarettes per day than whites, their smoking patterns and choices of brands may provide the nicotine content necessary to maintain daily blood nicotine levels similar to whites (Chapter VII; Cummings, Giovino, Mendicino 1987). Across all race and age categories, females report smoking fewer cigarettes than males. In the over 35 age groups this difference is approximately 20 percent.

Successful quitting behavior may not be uniform across all smokers. Heavy smokers (defined as those who report smoking 25 or more cigarettes per day) are more likely to have a strong nicotine dependence (Chapter IV) and, therefore, are less likely to be successful at quitting than lighter smokers. Thus, one would expect the cross-sectional surveys over time to indicate an increasing proportion of heavy smokers as the smoking prevalence declined. These data from self-reported consumption measures are presented in Table 10. The percentage of heavy smokers reported by the 1965 survey may be biased due to the use of proxy interviews which were not used in subsequent surveys.

Between 1976 and 1985, there was no substantial change in the proportion of smokers reporting smoking 25 or more cigarettes per day. In 1985, approximately one-third of all male smokers and one-fifth of all female smokers were classified as heavy smokers. Three times as many white as black adults were classified as heavy smokers. For both males and females, the proportion peaked in the group aged 35 to 44, possibly indicative of a higher mortality rate among older smokers.

Trends in Quitting Activity

Public health efforts to reduce the prevalence of smoking concentrate on reducing the proportion of the population that begins to smoke cigarettes as well as increasing the proportion of smokers who quit. One indicator of quitting activity is the prevalence of former smokers. However, this variable is of limited use due to marked
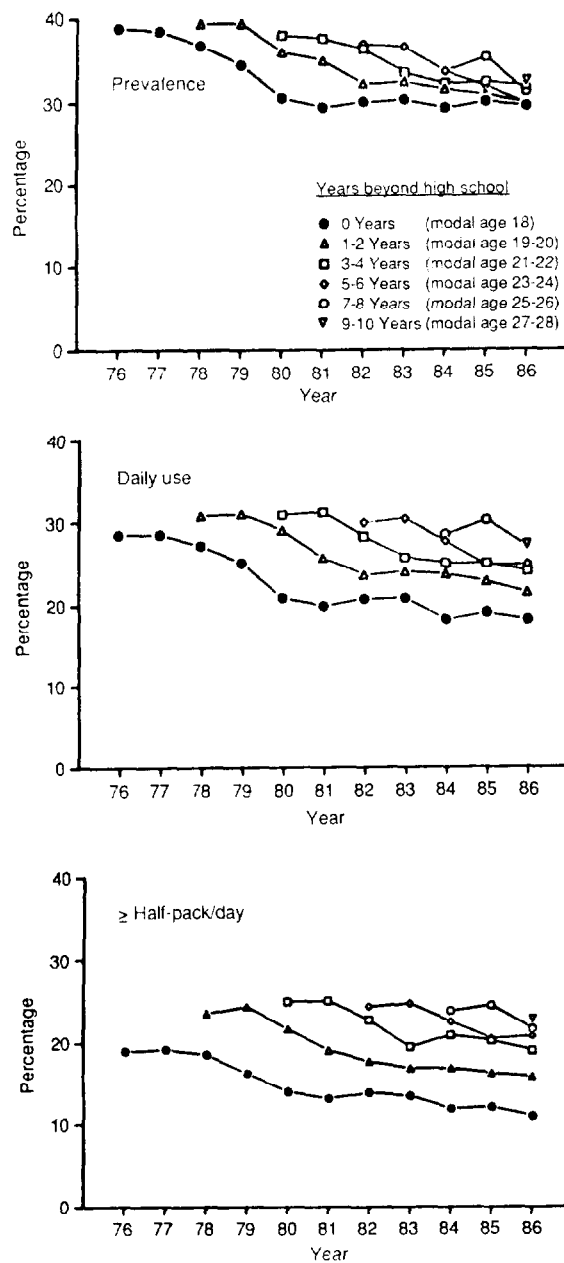
FIGURE 3.—Trends in 30-day cigarette smoking prevalence, daily use, and use of a half-pack or more per day among young adults, by age group

SOURCE: Johnston, O'Malley, Bachman (1987).

TABLE 9.—Average number of cigarettes smoked per day by current smokers, by race, age, and sex, United States, 1985

Race/Age	Men	Women	Difference
All races	21.8	18.1	3.7
Blacks	14.7	13.5	1.2
Whites	23.4	19.1	4.5
Age			
18–24	17.2	15.3	1.9
25–34	20.3	18.0	2.3
35–44	24.3	20.1	4.2
45–54	24.7	19.9	4.8
55–64	23.9	18.0	5.9
≥ 65	20.2	16.0	4.2

SOURCE: National Center for Health Statistics, National Health Interview Survey 1985.

TABLE 10.—Twenty-year trends in the proportion of smokers reporting smoking 25 or more cigarettes per day, by sex, race, and age, United States

Sex, race, age	1965	1976	1980	1985
Men				
Total	24.1	30.7	34.2	32.8
Race				
White	26.0	33.3	37.3	36.5
Black	8.6	10.8	13.8	10.7
Age				
20–24	15.4	18.5	19.8	17.1
25–34	24.3	28.7	30.1	28.5
35–44	31.5	39.2	40.7	42.3
45–64	28.0	37.4	42.6	39.3
≥ 65	13.8	18.2	25.2	25.4
Women				
Total	13.0	19.0	23.2	20.6
Race				
White	13.9	20.9	25.2	22.8
Black	4.6	5.6	8.6	6.7
Age				
20–24	9.7	14.5	15.9	12.2
25–34	15.5	20.5	24.2	21.3
35–44	17.1	21.8	32.7	27.8
45–64	13.6	21.5	24.9	22.7
≥ 65	6.4	11.8	13.1	13.4

SOURCE: National Center for Health Statistics, National Health Interview Surveys 1965, 1976, 1980, 1985.

differences in uptake of cigarettes between males and females in different birth cohorts (Warner and Murt 1982). A more meaningful index of quitting behavior has been defined as the quit ratio (Pierce, Aldrich et al. 1987)–the proportion of former smokers in a given population divided by the proportion of that population who have ever been smokers.

Trends in this quit ratio are presented in Figure 4. The quit ratio has consistently been higher among men compared with women. Quit ratios among both males and females increase with age. In 1985, nearly one-third of those persons aged 25 to 34 who reported that they had ever smoked had quit smoking by 1985. Among those aged 65 or older, the quit ratio was over 60 percent for women and 70 percent for men. Moreover, over the last 20 years, successful quitting activity has been increasing in all age groups. The quit ratio differences between men and women increased with age from 1965 to 1985 (several possible explanations for this phenomenon exist; see Chapter VII).

### Trends in Cigar, Pipe, and Roll-Your-Own Cigarette Smoking

Figure 5 shows 20-year trends in pipe and cigar smoking among adult males. For both tobacco products, there has been an 80 percent decline in prevalence. In fact, cigar smoking in 1964 (30 percent) was as prevalent as cigarette smoking in 1985 (30.4 percent).

Hand-rolled cigarettes are the least expensive cigarettes to consume. According to the 1986 Adult Use of Tobacco Survey, only 0.4 percent of smokers aged 17 and older use roll-your-own cigarettes (US DHHS 1988).

Trends in Smokeless Tobacco Use

The prevalence of both snuff and chewing tobacco use by younger men has increased substantially between 1970 and 1986, as shown in Figure 6. Among women, use of smokeless tobacco products decreased between 1970 and 1986, but prevalence of use in this group has always been low. In 1986, less than 0.4 percent of females used snuff or chewing tobacco, whereas 8.2 percent of men used these products (Novotny and Lynn, in press). Additionally, among men, almost half of current users reported initiation of smokeless tobacco use before age 17 (Table 11).

In 1985, the NIDA National Household Survey of persons 12 years of age and older found that 12 percent of men and 1 percent of women used chewing tobacco, snuff, or other kinds of smokeless tobacco in the year of the survey. Smokeless tobacco use rates were highest among young males (12–25 years old) who were residents of nonmetropolitan areas (Rouse, in press).

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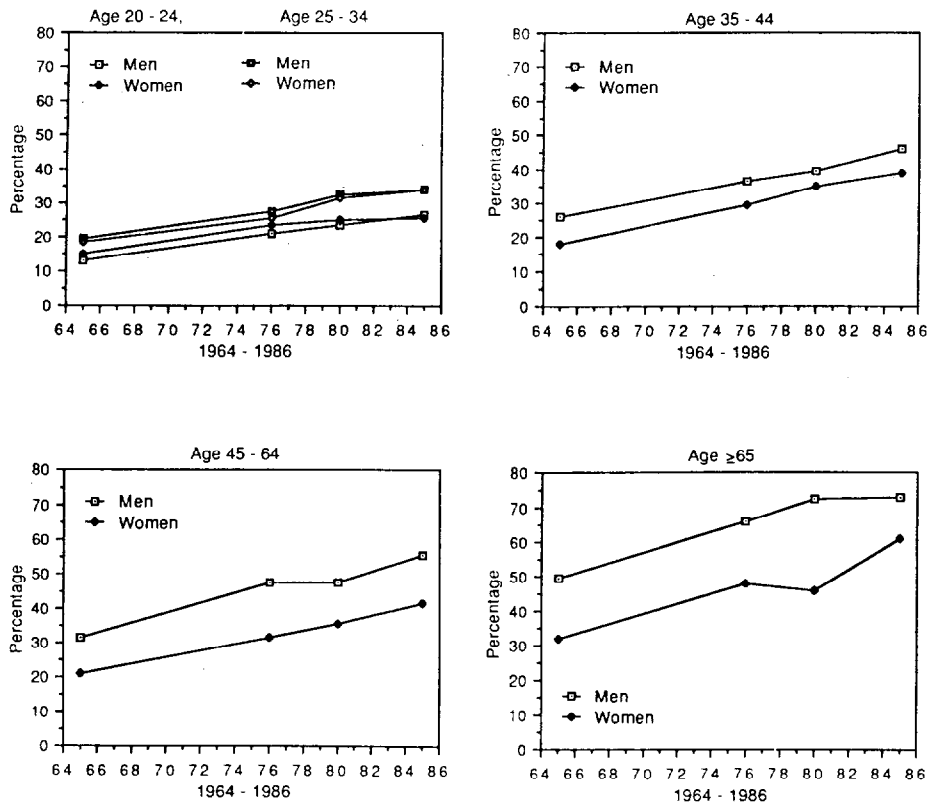
FIGURE 4.—Quit ratios (ratios of former smokers to ever smokers), by age and sex, 1965–1985

SOURCE: U.S. DHHS (1986b).

The BRFSS collected data from 25 States and the District of Columbia in 1986. In this survey, smokeless tobacco use among men ranged from 0.7 percent in New York to 21.4 percent in West Virginia (median State prevalence, 6.5 percent) (US DHHS 1987b). In addition, there was a regional pattern of use, with highest
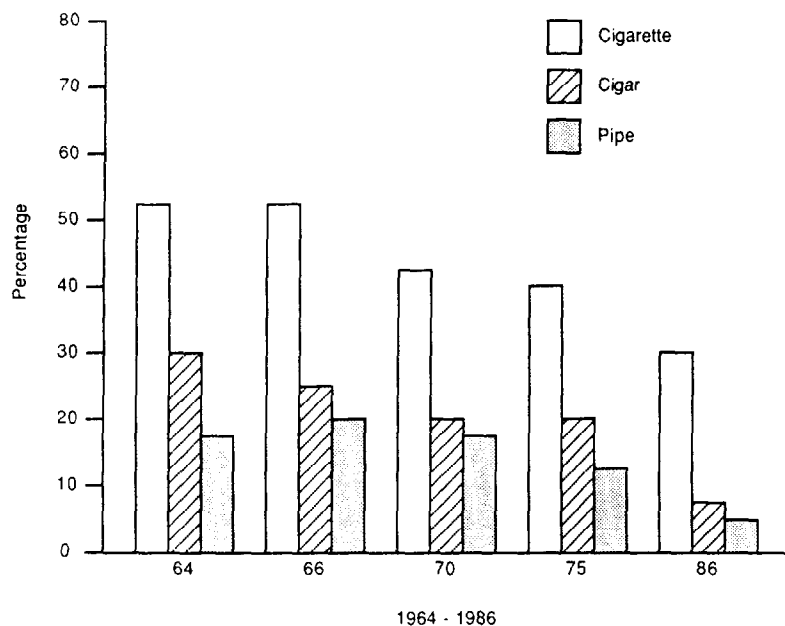
FIGURE 5.—Trends in prevalence of cigarettes, cigars, and pipes, adult men, 1964–1986

SOURCE: U.S. PHS (1970, 1975, 1986), U.S. DHHS (1987a).

prevalence found in Southern and North Central States, just as in the NIDA survey mentioned above.

Summary and Conclusions

1. An estimated 32.7 percent of men and 28.3 percent of women smoked cigarettes regularly in 1985. The overall prevalence of smoking in the United States decreased from 36.7 percent in 1976 (52.4 million adults) to 30.4 percent in 1985 (51.1 million adults).

2. In 1985, the mean reported number of cigarettes smoked per day was 21.8 for male smokers and 18.1 for female smokers.

3. Smoking is more common in lower socioeconomic categories (blue-collar workers or unemployed persons, less educated persons, and lower income groups) than in higher socioeconomic categories. For example, the prevalence of smoking in 1985 among persons without a high school diploma was 35.4 percent, compared with 16.5 percent among persons with postgraduate college education.

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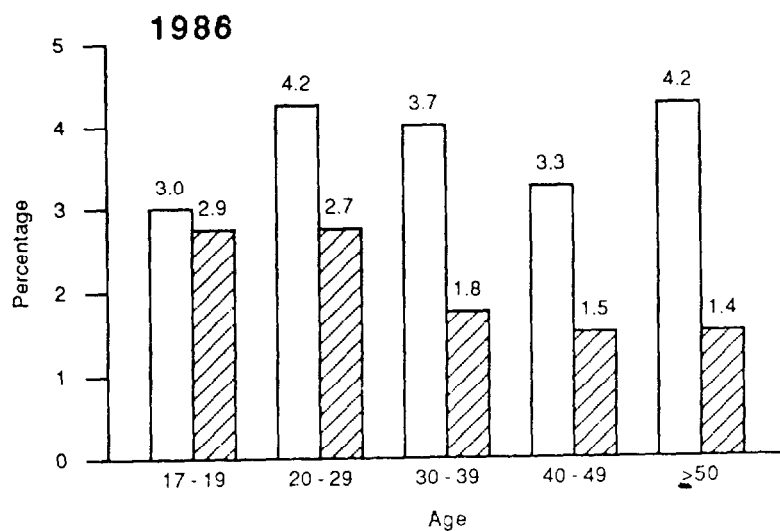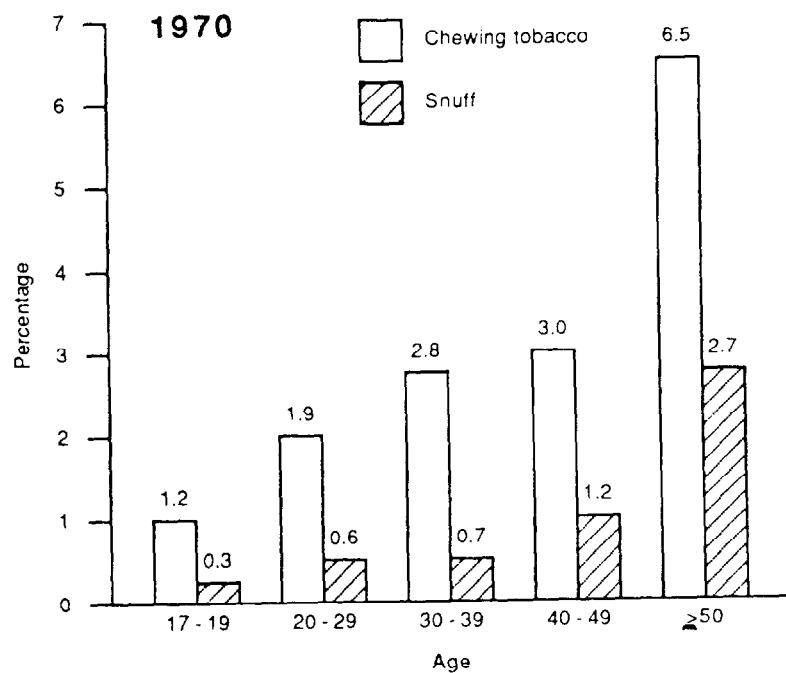
FIGURE 6.—Prevalence of chewing tobacco and snuff use among men, 1970 and 1986

TABLE 11.—Reported age at initiation, by current smokeless tobacco users (percentage), both sexes, 1986, United States

Age at initiation	Any smokeless tobacco	Chewing tobacco	Snuff
< 17 years	44.3	42.5	43.5
17-24 years	37.9	27.3	35.1
≥ 25 years	17.8	30.2	21.4

SOURCE: Novotny and Lynn. (in press).

4. An estimated 18.7 percent of high school seniors reported daily use of cigarettes in 1986. The prevalence of daily use of one or more cigarettes among high school seniors declined between 1975 and 1986 by approximately 35 percent; the smoking prevalence among females has consistently been slightly higher than among males. Most of the decline occurred between 1977 and 1981.
5. The use of cigars and pipes has declined 80 percent since 1964.
6. Smokeless tobacco use has increased substantially among young men and has declined among older men since 1975. An estimated 8.2 percent of 17- to 19-year-old men were users of smokeless tobacco products in 1986.

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APPENDIX B

TOXICITY OF NICOTINE

CONTENTS

Introduction

Knowledge of the toxicity of nicotine is important to help understand tobacco-induced human disease as well as to assess the potential risks associated with the therapeutic use of nicotine (e.g., nicotine polacrilex gum) as an aid to assist smoking cessation.

This Appendix provides a brief overview of the toxic actions of nicotine per se, focusing on human studies wherever possible and selecting only those animal data which have direct implications in understanding mechanisms of human disease. The toxicity of cigarette smoke has been extensively reviewed in prior Surgeon General's reports (US DHHS 1982, 1983, 1984, 1985, 1986). In most cases the pathogenesis of tobacco-related diseases, including the role of nicotine, has not been fully elucidated. Therefore the potential contribution of nicotine to development of tobacco-related disease, even if unproved, will be considered.

The chemistry and general pharmacology of nicotine have been reviewed in previous chapters (Chapters II and III) of this report and are not presented in detail in this Appendix. An appreciation of the basic pharmacologic actions of nicotine is, however, a necessary foundation for understanding the issues of toxicity which are discussed in this Appendix.

Acute Intoxication

As discussed in Chapter II, nicotine is a water and lipid soluble drug which, in the free base form, is readily absorbed via respiratory tissues, skin, and the gastrointestinal tract. Nicotine may pass through skin or mucous membranes when in alkaline solutions, in which circumstance nicotine is primarily un-ionized.

In experimental animals, the dose of nicotine which is lethal to 50 percent of animals (LD_{50}) varies widely, depending on the route of administration and the species used. Intravenous (i.v.) LD_{50} doses of nicotine in mice range between 0.3 to 1.8 mg/kg body weight (Borzelleca, Borman, McKennis 1962; Lindner 1963; Wirth and Gosswald 1965; Barlow and McLeod 1969). The intraperitoneal (i.p.) LD_{50} values for nicotine bitartrate in mice and rats have been found to be 13 and 83 mg/kg body weight, respectively, while the values for five inbred hamster strains varied between 125 to 320 mg/kg body weight (Bernfeld and Homburger 1972). The wide variation in sensitivity to the toxic effects of nicotine in rodents appears to be genetically determined (Garg 1969; Marks, Burch, Collins 1983; Miner, Marks, Collins 1984).

In interpreting animal toxicity data it is important to recognize that the rate of administration is an important determinant of toxicity. Rapid i.v. injections result in the highest blood and brain concentrations and produce toxicity at the lowest doses. In contrast,

with oral or i.p. administration higher doses are required to produce toxicity. This is due to presystemic ("first pass") metabolism of nicotine and the gradual time course of absorption as compared with after i.v. dosing. With intermittent dosing, such as practiced by smokers, the total dose of nicotine absorbed per day could exceed the toxic or even lethal dose of a single injection.

In humans, acute exposure to nicotine even in low doses (similar to the amounts consumed by tobacco users) elicits autonomic and somatic reflex effects as described in detail in Chapters II and III. Dizziness, nausea, and/or vomiting are commonly experienced by nonsmokers after low doses of nicotine, such as when people try their first cigarette. However cigarette smokers rapidly become tolerant to these effects (Chapter II).

A number of poisonings and deaths from ingestion of nicotine, primarily involving nicotine-containing pesticides, have been reported in humans (Beeman and Hunter 1937; McNally 1923; Franke and Thomas 1936; Saxena and Scheman 1985). The lethal oral dose of nicotine in adults has been quoted to be 40 to 60 mg (Goldfrank, Melinek, Blum 1980; Larson, Haag, Silvette 1961), but it has not been well documented. Nicotine intoxication produces nausea, vomiting, abdominal pain, diarrhea, headaches, sweating, and pallor. More severe intoxication results in dizziness, weakness, and confusion, progressing to convulsions, hypotension, and coma. Death is usually due to paralysis of respiratory muscles and/or central respiratory failure.

Dermal exposure to nicotine can also lead to intoxication. Such exposures have been reported after spilling or applying nicotine-containing insecticides on the skin or clothes (Lockhart 1933; Faulkner 1933; Benowitz et al. 1987) and as a consequence of occupational contact with tobacco leaves.

Green tobacco sickness, an occupational illness in field workers harvesting tobacco leaves, has been attributed to dermal absorption of nicotine found in the dew on tobacco leaves (Weizenecker and Deal 1970; Gehlbach et al. 1974). The levels of cotinine in the urine of exposed workers exceed those of novice smokers who had smoked three cigarettes in succession (Gehlback et al. 1975). The symptoms of green tobacco illness are described in Table 1 (Gehlbach et al. 1975; Gehlbach, Williams, Freeman 1979). A similar syndrome has been reported in Asian Indian tobacco workers who harvest green tobacco leaves and handle cured tobacco (Ghosh et al. 1979).

Tobacco harvesters who use tobacco products, either in the forms of cigarettes or smokeless tobacco, are usually not affected by green tobacco sickness owing to development of tolerance to nicotine (Gehlbach et al. 1974). Tolerance to the toxic effects may even develop during the course of nicotine poisoning, despite the persis-

TABLE 1.—Symptoms of systemic nicotine poisoning (Green Tobacco Sickness)

Symptom	Percentage (53 cases)
Nausea, vomiting	98
Pallor	89
Weakness	81
Dizziness, lightheadedness	81
Headache	81
Sweating	56
Abdominal pain	42
Chills	36
Increased salivation	17

SOURCE: Adapted from Gehlbach et al. (1974).

tence of nicotine in the blood at extremely high concentrations (200 to 300 ng/ml) (Benowitz et al. 1987).

Acute intoxication may occur in children following ingestion of tobacco materials. Four children, each of whom ingested two cigarettes, developed salivation, vomiting, diarrhea, tachypnea, tachycardia, and hypertension within 30 min; followed by depressed respiration and cardiac arrhythmia within 40 min; and convulsions within 60 min (Malizia et al. 1983). All recovered and suffered no complication. Another six children who ingested one-half of a cigarette experienced salivation and vomiting only. In a Swedish report (Werner 1969), 355 children who ingested tobacco had only very mild symptoms. Severe poisoning has occurred in children who swallowed tobacco juice (expectorated by tobacco chewers). Although ingestions of tobacco are common, deaths due to ingestion of tobacco are extremely rare, due to early vomiting and first pass metabolism of the nicotine which is absorbed.

Conceivably, intoxication from nicotine polacrilex gum could occur after accidental use by children or nonsmokers, or if an ex-smoker gum-user consumed several pieces at once or in rapid succession. One case report describes a smoker who developed apparent symptoms of nicotine intoxication within 1 min of chewing a piece of 2-mg gum (Mensch and Holden 1984). However, based on the known absorption kinetics and the amount of nicotine in the gum, true nicotine intoxication is unlikely in this case.

Swallowing nicotine polacrilex gum appears not to be of concern for development of toxicity. Although 30 to 85 percent of the nicotine content can be released from the gum into the gastrointestinal tract, the chances of nicotine intoxication are quite low because nicotine is

released slowly (transit time of the gums through the gastro-intestinal tract is 16 to 48 hr) (Brantmark and Fredholm 1974), and because the nicotine which is released undergoes extensive presystemic metabolism. Simultaneous ingestion of 10 unchewed pieces of 4-mg gum resulted in a peak blood concentration of nicotine of less than 10 ng/ml (Brantmark and Fredholm 1974), which is similar to the level attained by a smoker after smoking a single cigarette.

Chronic Nicotine Toxicity

As attested to in the Surgeon General's reports since 1964, smoking causes coronary and peripheral vascular disease (1983), cancer (1982), chronic obstructive lung disease (1984), peptic ulcer disease, and reproductive disturbances, including prematurity (1980). Tobacco smoke is a complex mixture of chemicals, including carbon monoxide, many of which have been implicated in human disease. Nicotine may contribute to tobacco-related disease, but direct causation has not been determined because nicotine is taken up simultaneously with a multitude of other potentially harmful substances that occur in tobacco smoke and smokeless tobacco.

However, particularly now that nicotine per se may be prescribed in the form of gum or other delivery systems, the potential health consequences of chronic nicotine exposure deserve careful consideration.

Cardiovascular Disease

Smoking causes coronary and peripheral vascular disease (US DHHS 1983). Both nicotine and carbon monoxide may contribute to atherosclerotic vascular disease (Figure 1). Nicotine could contribute both to the atherosclerotic process and to acute coronary events by several mechanisms. Nicotine could promote atherosclerotic disease by its actions on lipid metabolism and coagulation, by hemodynamic effects, and/or by causing endothelial injury. Compared to nonsmokers, cigarette smokers have elevated low-density (LDL) and very-low-density lipoproteins (VLDL), as well as reduced high-density lipoprotein (HDL) levels (Criqui et al. 1986; Brischetto et al. 1983), a profile associated with an increased risk of atherosclerosis. Chronic oral nicotine feeding has been shown to increase LDL in monkeys (Cluette-Brown et al. 1986). In one patient the use of nicotine polacrilex gum was reported to increase serum total and LDL cholesterol and triglycerides (Dousset, Gutierres, Dousset 1986). Nicotine may act by releasing free fatty acids, enhancing the conversion of VLDL to LDL, impairing the clearance of LDL and/or by accelerating the metabolism of HDL (Brischetto et al. 1983; Cluette-Brown et al. 1986; Gnasso et al. 1986; Hojnacki et al. 1986).

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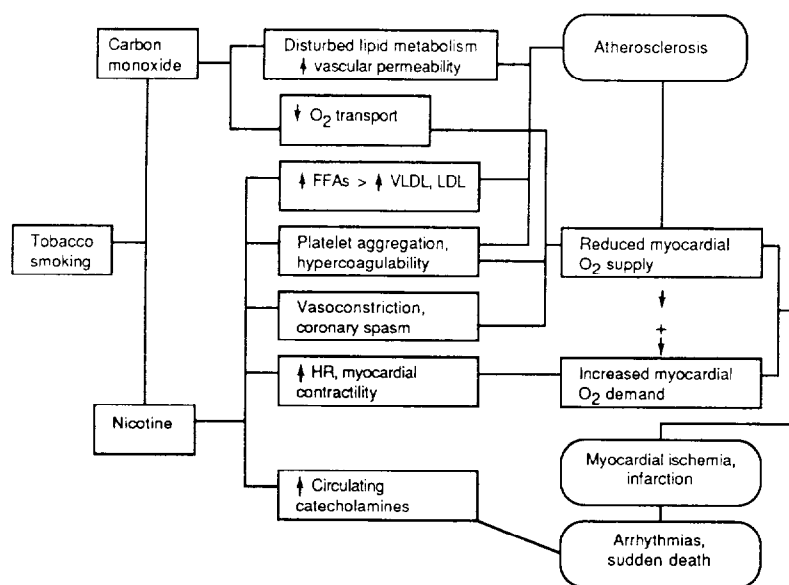
FIGURE 1.—Smoking, nicotine, and coronary heart disease
SOURCE: Benowitz (1986d).

Thrombosis is believed to play an important role in atherogenesis (Mehta and Mehta 1981). Platelets may release a growth hormone which promotes the growth of vascular endothelial cells, contributing to the atherosclerotic plaque (Packham and Mustard 1986). The blood of smokers is known to coagulate more readily than the blood of nonsmokers (Billimoria et al. 1975). According to several studies, platelets of smokers are more reactive, and have a shorter survival than those of nonsmokers (Belch et al. 1984; Siess et al. 1982; Mustard and Murphy 1963). The importance of nicotine as a determinant of platelet hyperaggregability is supported by a study showing that the blood concentrations of nicotine, after smoking different cigarettes, correlated with the platelet aggregation response (Renaud et al. 1984). Nicotine could affect platelets by increasing the release of epinephrine, which is known to enhance platelet reactivity, by inhibiting prostacyclin, an antiaggregatory hormone secreted by endothelial cells, or perhaps directly (Cryer et al. 1976; Sonnenfeld and Wennmalm 1980). Alternatively, by increasing heart rate and cardiac output and thereby increasing blood turbulence or by direct action nicotine may promote endothelial injury.

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Structural damage and increased mitotic activity in the aortic endothelial cells of nicotine-treated animals have been reported (Booyse, Osikowicz, Quarfoot 1981; Zimmerman and McGeachie 1985, 1987). Nicotine has also been shown to modulate the structural and functional characteristics of cultured vascular cells (Csonka et al. 1985; Thyberg 1986). In rats, nicotine given i.v. or per os p.o. produced dose-dependent increases in circulating anuclear carcasses of endothelial cells (Hladovec 1978). In support of the relevance of animal or in vitro studies to humans, Davis and colleagues (1985) reported an increase in the number of endothelial cells found in venous blood (reflecting endothelial injury) and a decrease in the platelet aggregate ratios (reflecting platelet aggregation) in non-smokers who smoked tobacco but not nontobacco (made from wheat, cocoa, and citrus plants) cigarettes.

The above findings suggest that some substance unique to tobacco, such as nicotine, may contribute to the pathogenesis of atherosclerosis and complications of atherosclerotic vascular disease. Although several potential mechanisms by which nicotine may promote atherogenesis have been considered, nicotine has not been demonstrated to produce or accelerate atherosclerosis in experimental animals. Wald and colleagues (1981) have presented an argument against the role of nicotine in promoting coronary heart disease in that pipe smokers, who consume comparable amounts of nicotine and have similar levels of nicotine but lower levels of carbon monoxide in the blood as cigarette smokers, do not share the same magnitude of increased risk for coronary heart disease. However, the possibility that nicotine inhaled in cigarette smoke, either due to rapid absorption or effects on pulmonary afferent nerves, affects the cardiovascular system differently than nicotine absorbed more slowly through mucous membranes must be considered (Benowitz and Jacob 1987).

Based on its pharmacologic actions, it is likely that nicotine plays a role in causing or aggravating acute coronary events. Myocardial infarction can be due to one or more of three precipitating factors – excessive oxygen and substrate demand, thrombosis, and coronary spasm. Nicotine increases heart rate and blood pressure and, therefore, myocardial oxygen consumption. Carbon monoxide inhaled in cigarette smoke reduces the oxygen carrying and releasing capacity of the blood. When a healthy person smokes a cigarette, coronary blood flow increases to meet the increased demand (Nicod et al. 1984). In the presence of coronary artery stenosis, coronary blood flow cannot increase and ischemia may develop, resulting in angina pectoris, myocardial dysfunction, or myocardial infarction (Jain et al. 1977). Nicotine may also directly reduce the increase in coronary blood flow which occurs in response to increased metabolic demand, or even cause an inappropriate decrease in coronary blood

flow, so that flow no longer matches increased myocardial oxygen consumption (Kaijser and Berglund 1985; Klein et al. 1984; Nicod et al. 1984; Martin et al. 1984). The decrease in coronary blood flow with smoking appears to result from alpha-adrenergically mediated coronary vasoconstriction, due to sympathetic activation and/or increased circulating catecholamines, either of which is likely to be an effect of nicotine (Winniford et al. 1986). Chronic nicotine exposure has been reported to increase the size of experimentally induced myocardial infarcts in dogs (Sridharan et al. 1985).

Nicotine consumed in the form of nicotine gum has been studied in patients with coronary artery disease. Nicotine gum (4-mg) increased myocardial contractility in healthy people, but in patients with coronary artery disease nicotine gum decreased contractility in the ischemic regions of the myocardium, consistent with aggravation of ischemia (Bayer, Bohn, Strauer 1985). In the most severe cases of coronary artery disease, overall contractility decreased after nicotine polacrilex gum. This study supports the idea that nicotine contributes to smoking-induced myocardial ischemia in susceptible people.

In addition to creating an imbalance between myocardial oxygen supply and demand, nicotine may promote thrombosis, as discussed previously. Nicotine may also induce coronary spasm by sympathetic activation or inhibition of prostacyclin. Coronary spasm has been observed during cigarette smoking (Maouad et al. 1984).

Sudden cardiac death in smokers might result from ischemia, as discussed above, combined with the arrhythmogenic effects of increased amounts of circulating catecholamines released by nicotine. However, smoking has not been demonstrated to increase the prevalence or magnitude of ventricular ectopy in patients with ischemic heart disease (Davis et al. 1985; Meyers et al. 1988). Cigarette smoking, most likely mediated by nicotine, facilitates AV nodal conduction, which could result in an increased ventricular response during atrial fibrillation (Bekheit and Fletcher 1976; Peters et al. 1988). Thus, even if the frequency of arrhythmias is not increased by smoking, the actions of nicotine may render those arrhythmias which do occur more life-threatening.

With respect to the arrhythmogenicity of nicotine, two case reports are of note. The first concerns a man who developed atrial fibrillation with a rapid ventricular response rate (150) while chewing 30 pieces of 2-mg nicotine polacrilex gum per day (Stewart and Catterall 1985). The other case was that of a man with known paroxysmal atrial fibrillation who developed a recurrence 5 min after chewing the day's first piece of nicotine gum (Rigotti and Eagle 1986).

Cigarette smoking has been associated with an increased risk of cardiomyopathy, that is a generalized reduction in contractility of

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heart muscle (Hartz et al. 1984). Cigarette smoke exposure induces cardiomyopathy in rabbits (Gvozdjáková et al. 1984). A role of nicotine is suggested by a study in which dogs received injections of nicotine for 22 months and developed impaired contraction of the heart muscle with evidence of some interstitial fibrosis on anatomical examination (Ahmed et al. 1976).

Exercise tolerance in patients with intermittent claudication improves after stopping cigarette smoking (Jonason and Bergström 1987; Quick and Cotton 1982). Nicotine could aggravate peripheral vascular disease by constricting small collateral arteries and/or by inducing local thrombosis. The effect of nicotine replacement therapy on symptoms of peripheral vascular disease, as on exercise tolerance, in comparison to cigarette smoking, requires further investigation.

On balance, short-term nicotine administration, such as nicotine replacement therapy as an adjunct to smoking cessation therapy, presents little cardiovascular risk to healthy individuals. Patients with coronary or peripheral vascular disease are likely to suffer some increase in risk when taking nicotine, but considerably less risk than with cigarette smoking, which exposes them also to both carbon monoxide and higher levels of nicotine.

Hypertension

Although cigarette smoking and nicotine per se increase blood pressure, cigarette smoking alone is not a risk factor for chronic hypertension (Green, Jucha, Luz 1986). Conceivably, factors such as lower body weight or altered dietary intake, which may be associated with cigarette smoking, might lower blood pressure to compensate for any blood pressure elevation due to nicotine.

However, progression of chronic hypertension to accelerated or malignant hypertension is much more likely in cigarette smokers (Isles et al. 1979; Petitti and Klatsky 1983). Nicotine could contribute to this progression by aggravating vasoconstriction, either via sympathetic activation or inhibition of prostaglandin synthesis. Animal studies indicate that nicotine may reduce renal blood flow which, in a patient with marginal renal blood flow due to hypertensive vascular disease, could cause renal ischemia and aggravate hypertension (Downey, Crystal, Bashour 1981). Thus, there is concern about nicotine replacement therapies in patients with severe hypertension.

Tobacco, most likely due to effect of nicotine, may interact with particular hypertensive diseases. For example, a patient with pheochromocytoma (a catecholamine-secreting tumor) developed paroxysmal hypertension and angina pectoris following the use of oral snuff (McPhaul et al. 1984). Within 10 min, blood pressure increased from 110/70 mmHg to 300/103 mmHg and heart rate from